TGF-beta2 secretion from RPE decreases with polarization and becomes apically oriented.

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Public Summary:
Age-related macular degeneration (AMD) is a leading cause of blindness in the elderly. In geographic atrophy, the late stage of the prevalent and untreatable dry form of AMD there is cell damage and cell death of the retinal pigment epithelium (RPE), a monolayer of cells immediately external to the light sensitive photoreceptors at the back of the eye. Since a major function of the RPE is to support function of the photoreceptors, loss of RPE leads to further degeneration of the photoreceptors and progressive blindness. Clinical trials are ongoing and are being planned for the use of embryonic stem cell derived RPE for the treatment of AMD. Trials are being designed using either subretinal injection of cell suspensions of stem cell-derived RPE or implantation of patches of monolayers of stem cell-derived RPE grown on a substrate. We have found that one of the growth factors secreted by stem cell-derived RPE is transforming growth factor-beta (TGF-beta). High levels of TGF-beta are associated with fibrosis and scarring while low levels have beneficial effects in outer retinal function. We found that cell suspensions of RPE expressed relatively high levels of TGF-beta and that levels became much lower and became directed towards the photoreceptor side of the RPE cell when the cells were in a polarized monolayer. There are similar levels of secretion of TGF-beta from primary RPE cultures and RPE derived from human embryonic stem cells. The authors conclude that low levels of TGF-beta expression could be a factor in favor of using RPE cell sheets rather than cell suspensions for the treatment of AMD.

Scientific Abstract:
Retinal pigmented epithelium (RPE) secretes transforming growth factor beta 1 and 2 (TGF-beta1 and -beta2) cytokines involved in fibrosis, immune privilege, and proliferative vitreoretinopathy (PVR). Since RPE cell polarity may be altered in various disease conditions including PVR and age-related macular degeneration, we determined levels of TGF-beta from polarized human RPE (hRPE) and human stem cell derived RPE (hESC-RPE) as compared to nonpolarized cells. TGF-beta2 was the predominant isoform in all cell culture conditions. Nonpolarized cells secreted significantly more TGF-beta2 supporting the contention that loss of polarity of RPE in PVR leads to rise of intravitreal TGF-beta2. Active TGF-beta2, secreted mainly from apical side of polarized RPE, represented 6-10% of total TGF-beta2. In conclusion, polarity is an important determinant of TGF-beta2 secretion in RPE. Low levels of apically secreted active TGF-beta2 may play a role in the normal physiology of the subretinal space. Comparable secretion of TGF-beta from polarized hESC-RPE and hRPE supports the potential for hESC-RPE in RPE replacement therapies.